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X-Linked Congenital Ataxia: A Clinical and Genetic Study

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We report on a family in which two males are affected with X-linked congenital ataxia (XCA). Clinical manifestations include severe hypotonia at birth, delay of early motor development, slow eye movements, and non-progressive cerebellar ataxia. The neurological examination excluded a neuromuscular disease, mental retardation, and pyramidal tract involvement. Neuroimaging showed global cerebellar atrophy in both patients that was not evident in the first years of life. The clinical findings in this family are very similar to those in a Russian pedigree [Illarioskin et al., 1996: Ann Neurol 40:75–83] and outline a recognizable phenotype. Linkage studies in our family, using 28 highly polymorphic Généthon microsatellite markers evenly distributed along the X chromosome, excluded a 24 cM interval between DXS990 and DXS424 located within the previous candidate region of 54 cM, reducing the critical interval. Am. J. Med. Genet. 92:53–56, 2000.

KEY WORDS: **X chromosome; congenital ataxia; cerebellar development**

INTRODUCTION

Congenital ataxias (CA) are genetically heterogeneous disorders characterized by severe hypotonia at birth, developmental delay, and neuroradiological evidence of global cerebellar atrophy without any other gross abnormality of the central nervous system [Ramaekers et al., 1997]. Inheritance can be autosomal dominant [Imamura et al., 1993], autosomal recessive [Guzzetta et al., 1993; Nystuen et al., 1996], or X-linked recessive [Young et al., 1987; Lutz et al., 1989; Illarioshkin et al., 1996], but the underlying molecular base remains unknown.

Linkage to chromosome 19p13.3 has been described in a recessively inherited form of CA associated with severe mental deficiency in a highly inbred population [Nystuen et al., 1996]. Another locus was mapped to a large genetic interval (54 cM) on Xp11.21-q24 in a Russian family with X-linked CA (XCA) [Illarioshkin et al., 1996]. We report on a second XCA family in whom two males shared clinical manifestations very similar to those reported in affected individuals from the Russian pedigree. We did a linkage study in our family further to define the genetic interval (54 cM) associated with XCA.

CLINICAL REPORT

Each family member was included in the genetic study after obtaining informed written consent. The propositus (III, 1) was first evaluated at age 1 year for delayed motor development. He was born at term after an uneventful pregnancy and delivery; weight at birth was 4,440 kg. Parents were unrelated and were healthy. Hypotonia, mild dysphagia, and delayed motor development were noted since birth. For instance, he could sit only with back support at age 9 months. At age 1 year, he was an alert boy, unable to sit unaided, and showed convergent strabismus. Deep tendon reflexes were normally evocable. Cranial circumference was 47.5 cm. Motor milestones were overall delayed: he was able to sit at 2.5 years, acquired sphincter control at age 3 years, and could stand with support at age 4 years, although he was ataxic. Pronunciation of words was achieved around the age of 1 year, but the speech was slurred. On neurological examination at 4 years, he showed normal tendon reflexes, no pyramidal signs, action tremor of upper limbs when attempting to reach for objects, and slow eye movements. At that time he manifested brief tonic fits without loss of consciousness. Electroencephalograms were repetitively normal. Electromyography of proximal muscles (right deltoid and vastus medialis) was normal. Somatosensory evoked responses (SSEPs) and neurography of the su-

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ral nerve and deep peroneal nerve were normal. Neuropsychological examination performed 6 months later showed normal cognitive abilities (IQ = 80) with some disability in learning procedures and in verbal fluency. Routine laboratory investigations were normal, including serum isoelectric focusing of transferrin. Brain MRI performed at age 2 years was normal, but a second MRI showed global atrophy of the cerebellum at age 3 years (Fig. 1A, B). The maternal uncle (II, 1) had had a similar course since birth and had been similarly delayed in achieving psychomotor skills. Over the course of several years, he showed unsteady gait and difficulty in standing unaided, which he achieved at age 8 years. When examined at age 36 years, he showed moderate dysarthria, unsteady gait with truncal and locomotor ataxia, intention tremor, limitation of vertical gaze with slow conjugate eye movements. SSEPs, motor evoked potentials, and brainstem evoked responses were normal. Brain MRI showed severe global atrophy of the cerebellar vermis and hemispheres (Fig. 1Ce,D). Neuropsychological examination showed no cognitive impairment; IQ was 82.

LINKAGE STUDY

Blood was collected from individuals shown in Figure 2 and total DNA was extracted using standard procedures. For genotyping, we used 28 highly polymorphic Généthon microsatellite markers, evenly distributed on the X chromosome and reported in Figure 2 [Dib et al., 1996]. PCR amplifications were performed as described by Gyapay et al. [1994]. PCR products were subjected to electrophoresis on a 6% denaturing polyacrylamide gel, transferred on to a nylon membrane, and then hybridized overnight at 42°C with ^{32}P dCTP labelled poly-C probes. DNA from CEPH subject N° 1347 was included in each experiment as a control for allele sizing.

Figure 2 summarizes the segregation of X chromosome haplotypes in this family. Exclusion mapping was

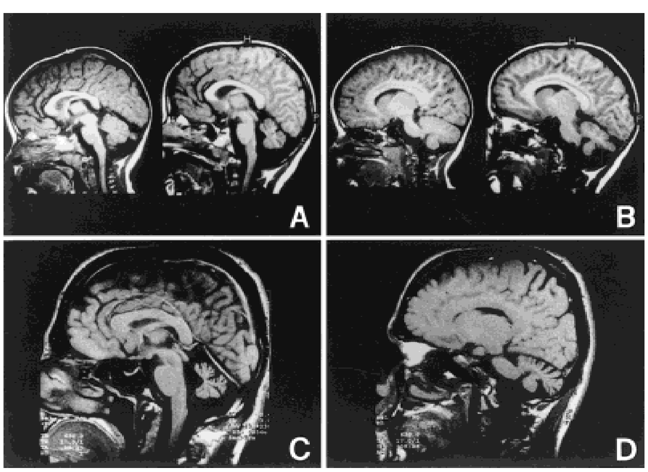

Fig. 1. Brain MRI longitudinal T1 weighted sections of the propositus and his uncle. Median section **(A)** and paramedian section **(B)** on the left sides correspond to the propositus at age 2 years; the right sides of A and B correspond to age 3 years. Notice progressive atrophy of the cerebellum with age. Median section **(C)** and paramedian section **(D)** show marked atrophy of cerebellar folia in the maternal uncle.

performed comparing the previously reported 54 cM region, flanked by markers DXS991 and DXS1001 [Illiarioskin et al., 1996], and our study. Haplotype analysis in our family refines the critical region to two subregions flanked by markers DXS991-DXS990 (20 cM) and DXS424-DXS1001 (10 cM), respectively.

DISCUSSION

We report the second family with XCA. Clinically two males in two subsequent generations were affected by delayed early motor development, cerebellar ataxia, dysarthria, lack of intellectual impairment, and limitation of gaze with slow eye movements. This association of symptoms was first described in a large X-linked pedigree by Illiarioskin et al. [1996] and mapped on Xp 11.21-q24. Differential diagnosis with other X-linked ataxias [Baraitser, 1997; Ramaekers et al., 1997] demonstrates the characteristic features of this condition defined by a nonprogressive course with the absence of other malformations or degenerations of the central and the peripheral nervous systems. A similar phenotype can be retrospectively recognized in a family described by Young et al. [1987] and in a large pedigree with a diagnosis of X-linked olivopontocerebellar atrophy [Lutz et al., 1989]. However, no linkage studies were done in those families. The absence of mental deficiency and limited eye movements differentiate XCA from the previously reported autosomal recessive families [Guzzetta et al., 1993], including those where a disease locus was mapped on chromosome 19p13.3 in a highly imbred population [Nystuen et al., 1996].

Brain MRI was initially normal in our propositus, despite ataxia had been evident since birth. At age 3 years, MRI disclosed a generalized cerebellar atrophy even though the child had improved in achieving his age's motor skills. These findings are new and suggest that cerebellar atrophy might be a consequence of a genetic disorder affecting the late developmental stages of the cerebellum [Goldowitz et al., 1998].

When we considered the striking similarities in clinical presentation between our patients and the Russian family, we adopted an exclusion mapping strategy by comparing our haplotype segregation analysis with data previously reported [Illarioshkin et al., 1996]. Exclusion mapping allowed us further to rule out a 24cM interval between DXS990 and DXS424, located within the reported candidate locus. It is, therefore, plausible that the XCA-gene lies on either Xp11.21-q21.3, between DXS991 and DXS990 (20cM), or Xq23-q24, between DXS424 and DXS1001 (10cM).

There is a recent report on a five-generation South African kindred in which 16 males are affected by a X-linked severe mental retardation, craniofacial dysmorphology, epilepsy, ophtalmoplegia, and cerebellar atrophy [Christianson et al., 1999]. Linkage studies show that the gene is located between markers DXS424 (Xq24) and DXS548 (Xq27.3) and to some extent it overlaps with one of our most distal candidate regions (DXS424-DXS1001). The clinical manifestations in this kindred are invariably characterized by generalized epilepsy and profound mental retardation that are clearly absent in our family as well as in the Russian

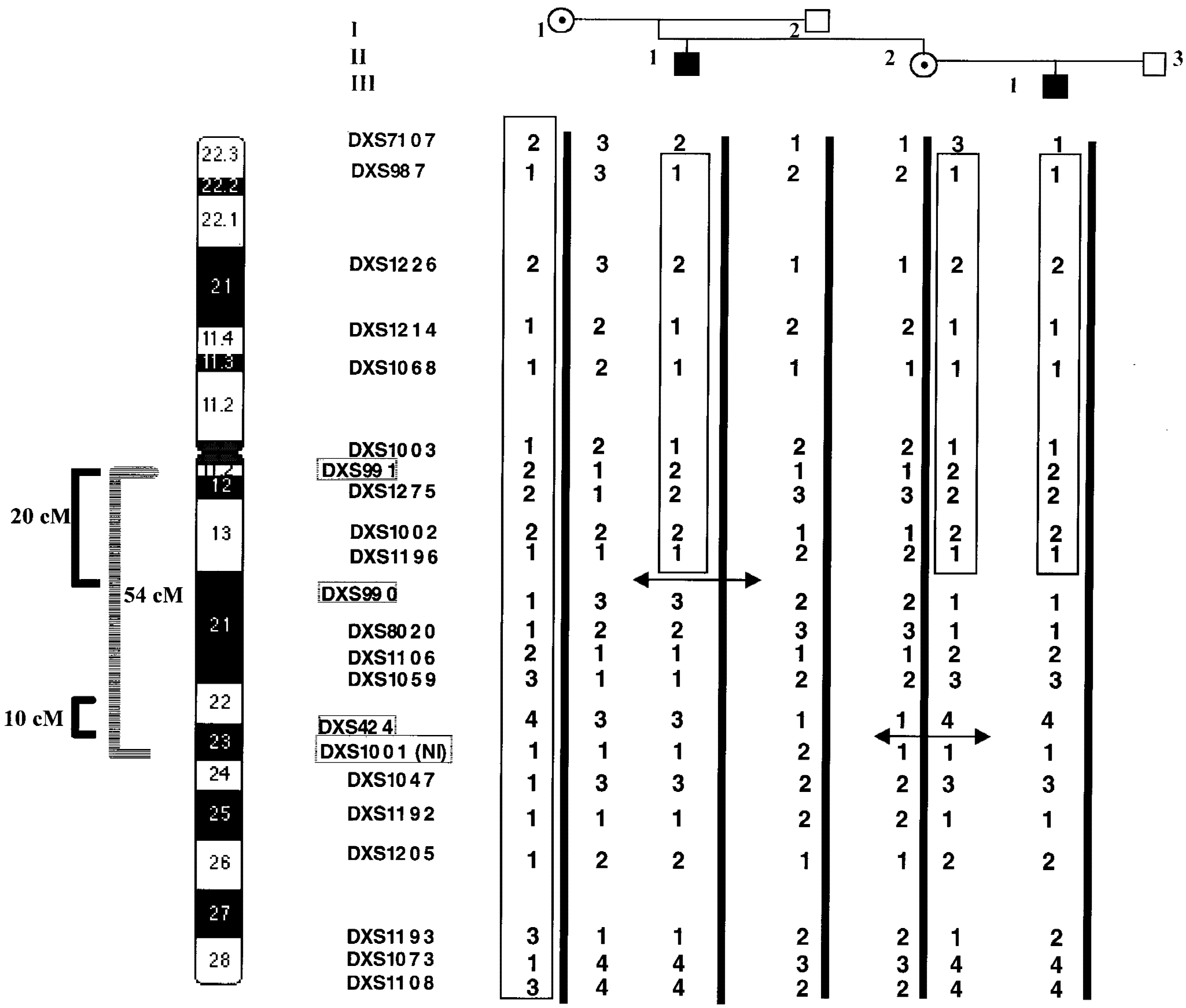

Fig. 2. Summary of genotyping results. An ideogram of the X-chromosome with approximate cytogenetic band positions is represented on the left. Markers used in this study are roughly localized according to the genetic map [Nagaraja et al., 1997]. Of the 28 polymorphic markers, only 21 informative markers are reported in the figure, with the addition of a noninformative (NI) marker (DXS1001) that limits one of the critical subregions. Double arrows indicate informative crossing-over events. The haplotypes that are shared by the hemizygous carriers and by the two affected males are outlined by squared boxes. The region selected by the multipoint linkage analysis of Illarioshkin et al. [1996] is represented on the left by a large gray parenthesis. Exclusion mapping in our study is represented by the two small black parenthesis on the far left. This reduces the critical region to two intervals flanked by DXS991-DXS990 and DXS424-DXS1001, respectively.

family. Although we cannot exclude that different mutations of a single gene located in this region might lead to various phenotypic consequences, we think that our family represents a distinct genetic disorder exclusively affecting cerebellar development. Alternatively, the XLMR families, reviewed by Christianson and coworkers [1999], could be the result of a contiguous gene syndrome. Further genetic analyses are necessary to narrow down the disease-gene locus, although this task may prove difficult because of the paucity of families.

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